Immunotherapy Overview, Rationale, and Role in Clinical Practice

OBJECTIVES
- Explain the relationship between cancer and the immune system
- Provide rationale for use of cancer immunotherapy with a specific focus on checkpoint inhibitors
- Contrast mechanisms of action, efficacy, and safety of current and emerging immune checkpoint inhibitors

Financial Disclosure
Bradi L. Frei, PharmD, BCOP, BCPS has no relevant financial relationships with commercial interests to disclose.

Relationship between Cancer and Immune System and Rationale for Cancer Immunotherapy

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IMMUNE SYSTEM

- Normally, the body’s immune system is able to detect and destroy abnormal cells

- Cancer cells avoid the immune system by
  - Reduced expression of antigens on the surface of the cell
  - Express proteins that induce immune system inactivation
  - Induce cells in the surrounding environment (microenvironment) to release substances that suppress immune responses and promote tumor cell proliferation and survival
  - Immune system has a blind spot

IMMUNOTHERAPY

- Stimulate the activities of specific components of the immune system
- Increase strength of immune system
- Counteract signals produced by cancer cells that suppress immune responses

FIRST USE OF IMMUNOTHERAPY

- von Behring and Wernicke found that animals could be cured of diphtheria
- An injection of sera produced by animals immunized with an attenuated form of diphtheria successfully treated a child with diphtheria
- Passive immunity

FIRST USE OF IMMUNOTHERAPY

- In 1891, William B. Coley (father of immunotherapy) injected bacteria into a patient with cancer
- Stimulated patient’s immune system and helped shrink patient’s tumor

TIMELINE FOR IMMUNOTHERAPY

1957 First report of allogenic stem cell transplant
1991 Characterization of human tumor associated antigens
1993 First study with IL-2
1995 Rediscovery of the regulatory of T cells
2010 Sipleucel-T and ipilimumab approved
2014 Blinatumomab, nivolumab, pembrolizumab approved

MECHANISM OF ACTION

TYPES OF IMMUNOTHERAPY

- Antibody-based therapies
  - Targeted monoclonal antibodies
  - Immune Checkpoint Regulation
  - Immunotoxin therapy
- Cancer Treatment Vaccines
- Adoptive Cell Therapy (ACT) - patient’s own immune cells are modified to target cancer cells and then re-administered to the patient
- Cytokines (IFN)
ANTIBODY BASED IMMUNOTHERAPY

- Antibody-based therapies
  - Targeted Monoclonal Antibodies
    - constructed from either human/murine chimeric or fully human antibody components that bind specific tumor-associated antigens, resulting in antibody-dependent cellular cytotoxicity (ADCC)
  - Immune Checkpoint Regulation
  - Immunotoxin Therapy

ANTIBODY BASED IMMUNOTHERAPY

- Antibody-based therapies
  - Targeted Monoclonal Antibodies
  - Immune Checkpoint Regulation
  - Immunotoxin Therapy

IMMUNE CHECKPOINT INHIBITORS

releases the “brakes” on the immune system, increasing its ability to destroy cancer cells

T CELL TARGETS

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IMMUNE CHECKPOINT INHIBITORS

IMMUNE SYSTEM

IPILIMUMAB MOA

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IMMUNE SYSTEM

• Cancer Treatment Vaccines
  • Made from a patient’s own tumor cells
  • Designed to treat cancers by strengthening the body’s natural defenses
  • Sipuleucel-T (Provenge®), for use in some men with metastatic prostate cancer.
  • Vaccines can be very expensive

IMMUNE SYSTEM

• Immune cell therapy/ adoptive cell transfer (ACT)
  • Tumor-infiltrating lymphocytes (TILs) with greatest recognition of tumor cells are collected
  • These cells are grown in the laboratory
  • Cells are activated by treatment with immune system signaling proteins called cytokines
  • Infused into patient

IMMUNE SYSTEM

• Therapeutic antibodies - made in lab are designed to cause the destruction of cancer cells
• Antibody-drug conjugates (ADCs)
• Chemically linking antibodies, or fragments of antibodies, to a toxic substance.
• Examples
  • ado-trastuzumab emtansine (Kadcyla®)
  • brentuximab vedotin (Adcetris®)

NAMING NOMENCLATURE

• Complicated but provides a lot of information
• Rituximab
  • the suffix -mab indicates that it is a monoclonal antibody
  • the substem -xi- denotes that it is of chimeric origin
  • the substem -tu- shows that it targets a tumor
  • and the prefix ri- is its individualized prefix

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**NAMING NOMENCLATURE**

<table>
<thead>
<tr>
<th>Substem a</th>
<th>Substem b</th>
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<tbody>
<tr>
<td>-b(a)-</td>
<td>bacterial</td>
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<tr>
<td>-c(i)-</td>
<td>cardiovascular</td>
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<td>toxin</td>
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<tr>
<td>t(u)</td>
<td>tumor</td>
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<tr>
<td>-v(i)</td>
<td>viral</td>
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<table>
<thead>
<tr>
<th>Naming scheme</th>
<th>A</th>
<th>B</th>
<th>x</th>
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<tbody>
<tr>
<td>rituximab</td>
<td>ri</td>
<td>tu</td>
<td>xi</td>
</tr>
</tbody>
</table>

**Action! Efficacy! Safety! of immune checkpoint inhibitors**

**Moa**

<table>
<thead>
<tr>
<th>Moa</th>
<th>Indications</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atezolizumab</td>
<td>NSCLC, Urothelial Carcinoma</td>
<td>1200 mg IV q 3 week</td>
</tr>
<tr>
<td>Ipilimumab</td>
<td>Adjuvant Melanoma, Metastatic Melanoma</td>
<td>10 mg/kg IV q 3 wks x 4, then 10 mg/kg q 12 wks for up to 3 years</td>
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<tr>
<td>Nivolumab</td>
<td>Renal Cell, NSCLC, Melanoma, Classical HL, SCCHN</td>
<td>240 mg q 2 week, 3 mg/kg q 2 week</td>
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<tr>
<td>Pembrolizumab</td>
<td>Melanoma, NSCLC, SCCHN</td>
<td>2mg/kg q 3 weeks, 200 mg q 3 weeks</td>
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### Safety

<table>
<thead>
<tr>
<th>Medicine</th>
<th>Common ADRs</th>
<th>Severe but less common ADRs</th>
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</thead>
<tbody>
<tr>
<td>Atezolizumab</td>
<td>Fatigue (52%), nausea (25%), pruritus (13%), musculoskeletal pain (15%)</td>
<td>Immune-mediated: AST (4%), ALT (4%), pneumonitis (3%), colitis (1%), and hepatitis (1%)</td>
</tr>
<tr>
<td>Ipilimumab</td>
<td>Fatigue (41%), diarrhea (32%), pruritus (31%), rash (29%)</td>
<td>Immune-mediated: enterocolitis (7%), hepatotoxicity (1%), endocrinopathy (4%)</td>
</tr>
<tr>
<td>Nivolumab</td>
<td>Fatigue (49%), musculoskeletal pain (32%), hyponatremia (35%), liver enzymes (~35%), rash (21%), pruritus (19%), cough (17%), upper respiratory infection (11%), peripheral edema (10%)</td>
<td></td>
</tr>
<tr>
<td>Pembrolizumab</td>
<td>Appetite (25%), fatigue (25%), nausea (20%), liver enzymes (~26%), rash (17%), pruritus (11%)</td>
<td></td>
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### TAKE HOME POINTS

- Cancer cells can manipulate the immune system to ‘hide’
- There are several targets for cancer immunotherapy
- Checkpoint inhibitors are effective in treatment of several kinds of cancer
- Dosing of checkpoint inhibitors differs depending on indication
- Checkpoint inhibitors are tolerated in most patients but a few patients will develop serious immune mediated reactions

We will always care for San Antonio. We will always educate healers. We will always search for answers.

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